6816 Wild Horse Court
Orangevale, CA 95662
(916) 989-5776
(916) 989-0552

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To:	Mathieu Vargot	**From:**	Randall F. Fuerst, OD
Fax:	1-571-273-8300	**Pages:**	7
Phone:	571-272-1211	**Date:**	14 September 2006
Re:	Application/Control Number: 10/735,451	**cc:**	

☐ **Urgent** x **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

• **Comments:**

Thanks for your review of the Office Action dated 15 May 2006.

In the United States Patent and Trademark Office
Office Action Response

Application/Control Number: 10/735,451
Art Unit: 1732

Applicants: Fuerst, et al.
Examiner: Mathieu D. Vargot

Title: Fabrication of improved contact lens using polymer electrospinning

Dear Mr. Vargot,

In response to the Office Action of 5/15/06, the Applicant respectfully submits the following:

Our patent application claims have been cited as conflicting conflict with the following prior art:

- Simpson, et al., US-2002/0090725
- Burgess et al., US-6,559,119

In regards to our (Fuerst et al) application, we would respectfully take issue with these two citations. Simpson et al describes an incorporeal use of electrospun fibers. Our patent articulates an "extracorporeal" use of electrospun fibers. Simpson et al does not describe an ex-vivo use in contact with an aqueous solution and the skin, as may describe a topical ophthalmic use such as a contact lens, so they imply any extra-corporeal use as being covered by their disclosure. If that were the case, then electrospun garments for example, which are ex-vivo and in contact with the body would be similarly restricted by their pending IP. In fact, electrospun materials of all types have been in use in the public domain for much of the 20th century, fabricated using a plethora of polymers. I argue that a refractive correction contact lens was not anticipated by Simpson et al and not intended as a scaffold for in vivo use, the electrospinning fabrication of which has been in the public domain for nearly a hundred years. Our novelty exists in the use of electrospun material for refractive correction and/or ex vivo therapeutic use, not as a scaffold, where fluid and gaseous diffusion surpass existing contact lens materials and fabrication methods. Additionally, our application is not just for collagen, but also current contact lens materials such as HEMA (hydroxyl ethyl methacrylate—the most commonly used soft contact lens material.)

Discussion

Simpson et al

The cited invention of Simpson et al describes "electroprocessing" as an all encompassing technology that includes electrospray, electrospinning, electrosputting, etc. (see claims 1-9, 11-14, 16-24). The applicant would like to respectfully bring to the attention of the examiner that co-inventor John Fenn, (2002 recipient of the Nobel Prize in Chemistry), won this prize for his work that began in the early 1980s, for creating gas phase ions of organic macromolecule—using electrospray. Such molecules include proteins and peptides. Further, such proteins and peptides represent long polymer chains, and therefore are in fact "fibers". On page 43988, Federal Register, 40, July 29, 2005,the definition of the aspect ration of a fiber (in this case, asbestos fibers) states "a particulate form of asbestos 5 micrometers (μm) or longer with a length-to-diameter aspect ratio of at least 3-to-1".

A fiber, as defined by the National Institute of Health, is a molecular species whose length is 3 times its' width. Thus, in truth, electrospray is a form of electrospinning. In fact, both the electrospray process and electrospinning have been practiced since the turn of the 20th century. One of the foremost authorities besides John Fenn, Ph.D., is Darrell Reneker, Ph.D. from the University of Akron. The process of electrospinning fibers from a multitude of materials has been well documented in the literature well before Simpson et al attempted to patent said.[1-7]
Our efforts, in light of numerous electrospun materials, is to patent the novel use of electrospinning to manufacture a contact lens. Our claim hinges upon the reality that electrospinning has been around for a number of years, but that no one has attempted to utilize this process for ophthalmic use, and more specifically, as a way to manufacture contact lenses. Electrospinning a contact lens is unique and novel, because the current process utilizing HEMA and silicon hydrogel begin with a solid button of material. Oxygen permeability depends on the porosity of the material. There is a never ending search for more materials that are able to provide good wettability concurrent with oxygen transmission through the lens material (Dk/t). The process of electrospinning nanofibers will provide interfibrillar spacing that will dramatically increase the flow of oxygen and, hence, a physiologically healthier contact lens.
Given the citation of Simpson et al, a little background is in order.

Electrospray Background

Electrospray has emerged as the predominant technique for producing intact ions in vacuo from large and complex species in solution. To an extent greater than has previously been possible with the more familiar "soft" ionization methods, this technique makes the power and elegance of mass spectrometric analysis applicable to the large and fragile polar molecules that play such a vital role in biological systems. The distinguishing feature of electrospray spectra for large molecules are coherent sequences of peaks whose component ions are multiply charged, the ions of each peak differing by one charge from those adjacent neighbors in the sequence. Spectra have been obtained for biopolymers including oligonucleotides and proteins, the latter having molecular weight up to and beyond 130,000, with as yet no evidence of an upper limit!

Mass spectrometry consists in "weighing" individual molecules by transforming them into ions in vacuo and then measuring the response of their trajectories to electric and magnetic fields, or both. Attempts to extend the sensitivity and accuracy of mass spectrometric methods to the analysis of large polar organic molecules of interest in biology and medicine have long been frustrated by the difficulties of transforming such molecules into gas-phase ions. They cannot be vaporized without extensive, even catastrophic, decomposition. Consequently, one cannot apply classical methods of ionization that are based on gas phased encounters of the molecule to be ionized with electrons as in electron ionization, or electronically excited atoms or molecules. Such encounters can remove a negatively or positively charged entity from a neutral molecule, or sometimes attach one, thus transforming it into a gas phase ion.

In the last 25 years, experimentalists have developed a number of so-called "soft" ionization methods that have been used with varying degrees of success to produce intact ions from molecular species of ever increasing size and decreasing vaporizability. One class of such methods is based on very rapid deposition of energy on a surface over which the species to be analyzed (analyte) has been dispersed. The underlying idea, first proposed by Beuhler et.al, is that sufficiently rapid energy input may bring about vaporization before decomposition has a chance to take place (1). The several methods differ in the way that rapid energy deposition is brought about. In plasma desorption (PD), it results from the impact of a fusion product of a radioactive isotope, usually Californium-252. So-called secondary ionization mass spectrometry (SIMS) makes use of an incident beam of high-energy ions, such as 40-keV and will therefore here be referred to here as fast ion bombardment (FIB). If the ions are neutralized by charge exchange before they strike the surface, FIB becomes FAB (for fast atom bombardment). In laser desorption (LD), photons are the vehicle for energy deposition. These "energy-sudden"

techniques have been able to produce intact ions from remarkably large analyte species, even though, in an overall sense, the processes involved are highly irreversible. Striking improvements have resulted from dispersing the analyte not on a bare surface but in a layer of suitable matrix, for example, thioglycerol for FAB or FIB, nitrocellulose for PD, and nicotinic acid for LD. At this writing the highest molecular weights of ions that have been produced are with LD 210,000; (2), with FAB (or FIB) 24,000; (3), and, (4) with PD 45,000. However, product ion currents are usually very small and, except in the case of LD, decrease rapidly with increasing molecular weight of the analyte.

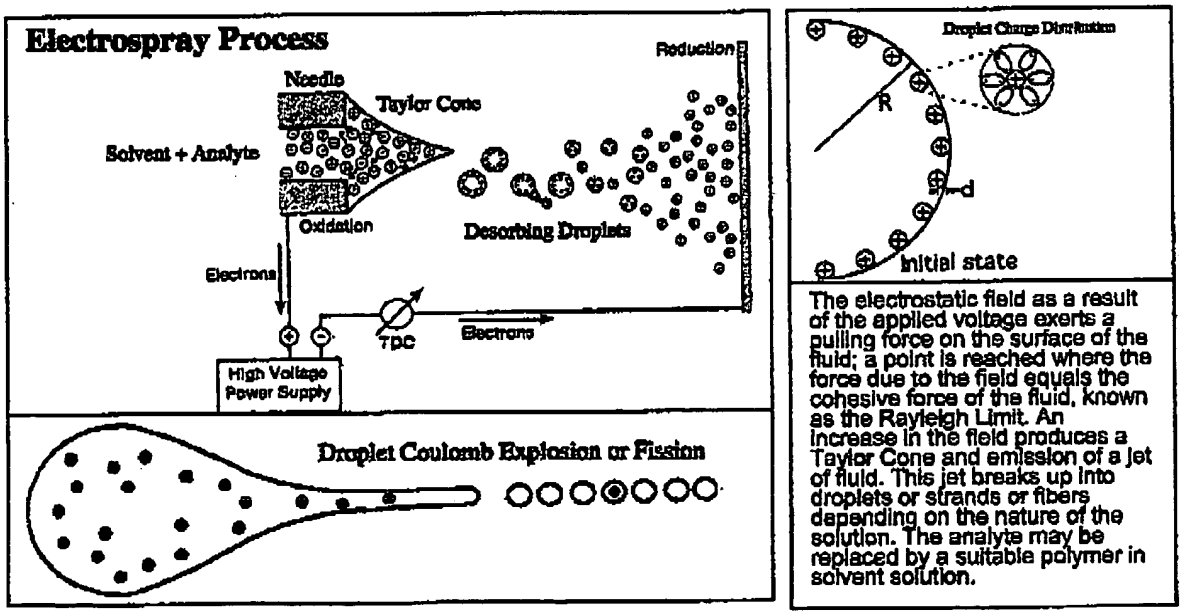
When the ions are very large, their detection with the multipliers requires post acceleration voltages that are sometimes awkwardly high. Furthermore, the ions often have high levels of internal excitation that can cause substantial peak broadening as a result of predissociation. Quite different in practice and principle from these "violent" ionization methods are techniques that use strong electrostatic fields to extract ions from a substrate. In so-called field desorption (FD) ionization, the analyte molecules are applied to a fine wire on whose surface is deposed an array of sharp pointed needles or "whiskers". When the wire is placed in a vacuum system and a high voltage is applied while it is carefully heated, the analyte molecules desorbs as ions from the tips of the needles where the field strength is very high (5). Even though it can transform highly nonvolatile analytes into ions in vacuo, FD has not been widely used because sample preparation is tedious. Finding and maintaining the combination of temperature and voltage that is right for a particular species requires both luck and the right touch. Finally, the desorbed ions have such high energies that relatively expensive magnetic sector analyzers must be used for their analysis. In electrohydrodynamic (EH) ionization, the analyte is dissolved in a nonvolatile liquid (for example, gylcerol) and injected into an evacuated chamber through a small capillary tube that is maintained at high voltage (6). The solvent liquid must have a low vapor pressure so that it will not "freeze-dry" from rapid evaporation into vacuum. Solute ions, along with molecules and clusters of solvent are desorbed from the emerging liquid by the high field at its surface and can be mass analyzed. EH, like FD, have not had many practitioners, in part because few liquids that have low vapor pressure are good solvents, and in part because the desorbed ions are usually solvated with one or more molecules of the solvent, and, lastly, because they often have a wide energy distribution. As in FD, the high ion energies in EH require magnetic sector analyzers.

What Exactly Is The Mechanism of Electrospray?

During World War I, John Zeleny did some experiments in which he passed a small flow of conducting liquid through a metal capillary tube or "needle" maintained at high potential relative to an opposing counter-electrode. The resulting intense field at the needle tip dispersed the emerging liquid into a fine spray of highly charged droplets. Zeleny also noted that as the droplets evaporated they became unstable and disrupted into a multiplicity of smaller droplets. Such instability had been predicted and characterized by Lord Rayleigh in 1883. He argued that evaporation of solvent would increase the charge density on the droplet surface until Coulomb repulsion would overcome the surface tension that held the droplet together.

The resulting "Rayleigh Instability" would disrupt the droplets into a multiplicity of smaller droplets. In 1968, Malcolm Dole suggested the small droplets resulting from such a Rayleigh instability would repeat this evaporation-disruption process. Dole's group later reported the production of gas phase ions of intact oligomers of polystyrene with molecular weights up to 500,000. Their approach was similar to Zeleny's, but with a few twists. The method was to introduce a dilute solution of the polymer in a volatile solvent through a hypodermic needle (with a conical tip) into a chamber through which nitrogen flowed at atmospheric pressure. A potential difference of several kilovolts between the needle and the chamber walls would produce an intense field at the needle exit and disperse the emerging liquid into a fine jet, yielding a spray of charged droplets that would drift down the field toward the end wall of the chamber. The electric

field pulls the solvent-analyte mixture outward, away from the needle tip in a similar fashion as a child pulls a piece of taffy apart. As the electric field overcomes the surface tension of the fluid, a "Taylor" cone is formed, so named in honor of Sir Geoffrey Ingram Taylor who first calculated the perfect conejet angle of 98.6° in 1964. A jet of fluid is emitted from the apex of the Taylor Cone which breaks up into a series of macro droplets. As the droplets evaporate, their surface charge density would increase until the Coulomb repulsion overcame the surface tension. (This is because like charges accumulate on the surface of the droplet. Since like charges repel one another, this results in instability or droplet fission to occur.) At this stage, the so-called Rayleigh limit, the resulting instability would break up the droplet into a plurality of smaller droplets, each of which would repeat the evaporation-to-instability sequence. If the original solution were sufficiently dilute, this sequence would lead to ultimate droplets small enough to contain only one macromolecule, which would retain some of the droplet charge to become an ion as the last solvent evaporated. What Dole did not know was that excess solvent was being carried with his target species into the vacuum chamber where adiabatic expansion caused the desolvated ions to be resolvated by the condensation of the solvent onto the ions, in essence creating flying chunks of ice. The resulting mass spectra did not, and could not, match that expected for monomers, dimers, trimers, etc. of the polymer-analyte. Fenn changed the bath gas from co-current to counter-current mode, increasing the desolvation of the ions and permitting full "Coulomb Explosion" or droplet fission-instability to transpire before being introduced into the high vacuum environment of the mass spectrometer.



One of the promising processes to produce nano-scale fibers is electrospinning. History of electrospinning process goes back to the early 1930s (Subiah et al., 2005). The main principle in electrospinning as defined by Doshi and Reneker (1995) is to generate a charged jet of polymeric solution by applying an electric field. As the jet travels in the air, the solvent evaporates and a charged fiber is left behind which can be collected on a metal screen. Through this process, mostly a mat of randomly oriented fibers with large surface area and pore sizes (as well as different fiber morphologies and geometries) are fabricated from various

polymer solutions, as noted in Deitzel et al (2001). There are recent review articles regarding electrospinning of nanofibers, such as Li and Xia (2004) and Subiah et al. (2005).
The resultant fiber size (diameter) and morphology by electrospinning has been studied as they determine several responses of the electrospun mat of fibers. Ataçay et al. (2004), for instance, have investigated the effect of morphology of the electrospun mat of PAN on the resultant hydrophobic behavior. They observed three different morphologies: beads only, beads-on-fibers, and fibers only.
Despite relatively early introduction of the electrospinning process (1930's), the effect of the process and material parameters on fiber formation and morphology of the thin film/mat is still under investigation.
http://www.executive-conference.com/conferences/archives/abstracts2005/nano05_abs1c.html

The process articulated by Simpson et al is for in vivo or incorporeal scaffolding use. The subject invention of Fuerst et al is extra corporeal and is intended for scaffolding, but as a biocompatible, minimally invasive, "contact" lens. As such, none of the art described in Simpson et al applies to a contact lens. As for the process to make a collagen lens, collagen is a polymer and the practice of electrospinning "polymers" has been in use since the turn of the 20th century.

In Vivo Utilization
Burgess et al
Burgess, et al., in their claim number 36, which reads (36. *The method of claim 1 or 2, wherein said biomedical material is selected from the group consisting of an orthopedic device, a urinary catheter, an intravascular catheter, a suture, a vascular prosthesis, an intraocular lens, a contact lens, a heart valve, a shoulder replacement device, an elbow replacement device, a hip replacement device, a knee replacement device, an artificial heart, a fixation plate, a dental implant, a nasal implant, a breast implant, a testicular implant, a sponge, a film and a bag.)* Our claim is to manufacture contact lenses. In claims 1 and 2, Burgess states that their patent is *1. A method of preparing a biomedical device intended for implantation into an animal's body and having a supplemented tissue sealant.* This method and process involves tissue sealant. Thus, while a tissue sealant could be added to the surface of a contact lens (as noted in claim 36), the manufacture of a contact lens using the novel approach of utilizing a solvent to dissolve the contact lens material, and then electrospinning this material into a super-porous mat for lathe cutting and/or laser edging is dramatically different.

Thank you for your consideration. We would (John Fenn, Ph.D., Joe Bango, MS, and Randall F. Fuerst, OD) appreciate the opportunity of a meeting to discuss this further.

Corresponding Address: 6816 Wild Horse Court, Orangevale, CA 95662-3453; Rfuerst@gmail.com

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